

Novartis Institutes for BioMedical Research

LHW090

Clinical Trial Protocol CLHW090X2202

**A randomized, sponsor open, site and subject double blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of LHW090 after 4 weeks treatment in patients with resistant hypertension**

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## **Site Operations Manual (SOM)**

A Site Operations Manual (SOM) accompanies this protocol, providing the operational details for study conduct.

### **Notification of serious adverse events**

Refer to [Section 9.2](#) of the protocol for definitions and reporting requirements for Serious Adverse Events (within 24 hours after awareness of the SAE to the local Novartis Drug Safety and Epidemiology Department and notify the Clinical Trial Leader.).

Contact information is listed in the Site Operations Manual.

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## List of abbreviations

ABPM	Ambulatory blood pressure monitor
ACE	Angiotensin-converting-enzyme
AE	Adverse event
ALT	Alanine aminotransferase
ALP	Alkaline phosphatase
ARB	Angiotensin Receptor Blocker
ASH/ISH	American Society of Hypertension and the International Society of Hypertension
ANP	Atrial natriuretic peptide
AST	Aspartate aminotransferase
BMI	Body Mass Index
BNP	B-type natriuretic peptide
BP	Blood pressure
CABG	Coronary artery bypass grafting
CD-ROM	Compact disc – read only memory
CNP	C-type natriuretic peptide
CFR	Code of Federal Regulation
cGMP	Cyclic guanosine monophosphate
CK	Creatine kinase
CRF	Case Report/Record Form (paper or electronic)
CRI	Chronic renal impairment
CRO	Contract Research Organization
C-SSRS	Columbia Suicide Severity Rating Scale
CV	Coefficient of variation
DDI	Drug-drug interaction
EC	Ethics committee
ECG	Electrocardiogram
EDC	Electronic Data Capture
ESC	European Society for Cardiology
FDA	Food and Drug Administration
FIH	First in human

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GCP	Good Clinical Practice
GFR	Glomerular filtration rate
h	hour
IC50	Half maximal inhibitory concentration
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT	Interactive Response Technology
LFT	Liver function test
LDH	lactate dehydrogenase
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
mg	Milligram(s)
ml	Milliliter(s)
NEP	Natriuretic peptides
NSAIDS	Nonsteroidal anti-inflammatory drugs
PA	Posteroanterior
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PK	Pharmacokinetic(s)
p.o.	Oral(ly)
RBC	Red blood cell(s)
REB	Research Ethics Board
RHT	Resistant hypertension
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SOM	Site operations manual
SUSAR	Suspected Unexpected Serious Adverse Reactions
TBL	Total bilirubin
TIA	Transient ischemic attack

ULN            Upper limit of normal

WBC            White blood cell(s)

WHO            World Health Organization

## Pharmacokinetic definitions and symbols

AUC0-t	The area under the plasma concentration-time curve from time zero to time 't' where t is a defined time point after administration [ng x hr / mL]
AUClast	The area under the plasma concentration-time curve from time zero to the time of the last quantifiable concentration [ng x hr / mL]
Cmax	The observed maximum plasma concentration following drug administration [ng / mL]
Tmax	The time to reach the maximum concentration after drug administration [hr]

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## Protocol synopsis

<b>Protocol number</b>	LHW090X2202
<b>Title</b>	A randomized, sponsor open, site and subject blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of LHW090 after 4 weeks treatment in patients with resistant hypertension
<b>Brief title</b>	Safety and efficacy study of LHW090 in resistant hypertension patients
<b>Sponsor and Clinical Phase</b>	Novartis Phase II
<b>Intervention type</b>	Drug
<b>Study type</b>	Interventional
<b>Purpose and rationale</b>	To determine whether LHW090 displays the clinical safety and efficacy profile to support further development in patients with resistant hypertension.
<b>Primary Objective(s)</b>	<ul style="list-style-type: none"><li>• To assess the safety and tolerability of LHW090 for 4 weeks on a background of conventional anti-hypertensive medications in patients with resistant hypertension.</li><li>• To evaluate the effect of LHW090 on placebo-adjusted mean daytime systolic blood pressure (SBP) after 4 weeks in patients with resistant hypertension.</li></ul>
<b>Secondary Objectives</b>	<ul style="list-style-type: none"><li>• To evaluate the pharmacokinetics (PK) of LHW090 and its active metabolite LHV527 in patients with resistant hypertension.</li></ul>
<b>Study design</b>	This is a non-confirmatory, randomized, sponsor open, site and subject blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of 4 weeks treatment with LHW090 in patients with resistant hypertension. Patients with uncontrolled hypertension as defined as a mean daytime systolic blood pressure $\geq$ 135 mmHg by ambulatory blood pressure monitoring (ABPM) on a stable (at least 1 month) regimen of an angiotensin receptor blocker (ARB) plus a diuretic plus at least one additional class of anti-hypertensive medication will be considered for this trial. Patients with resistant hypertension will be randomized to either placebo or 1 of 2 dose regimens of LHW090, i.e. LHW090 100 mg once daily or LHW090 200 mg once daily, as an add-on to their anti-hypertensive regimen at baseline.  Each subject will participate in an approximately 3 week screening period, a 2-week single blind placebo run-in period, baseline assessments, a 4 week treatment period, and an end of study assessment. During the 2 week placebo run-in period, patients will receive regular reminders to be compliant with their anti-hypertensive medications. At the end of this run-in period, patients who demonstrate $\geq$ 80% compliance with placebo will be randomized. Compliance will be established by pill count and review of medication diary. Subjects will be advised that study entry cannot be fully determined until the completion of the run-in period.

	<p>On Day -2, patients will commence 24 hour ABPM monitoring and return the next day (Day -1) to have the ABPM device removed and the data collected. Patients may have additional attempts to complete a successful ABPM assessment (defined by satisfactory BP data sampling over the 24 hours and standards for device quality check) if the first attempt is unsuccessful (<a href="#">O'Brien et al 2013</a>). Upon collection of satisfactory baseline ABPM assessment, subjects will then return for baseline pharmacodynamic assessments on Day -1 and then begin active treatment on Day 1. Patients will be randomized to either:</p> <ul style="list-style-type: none"><li>• LHW090 100 mg once daily for 28 days</li><li>• LHW090 200 mg once daily for 28 days</li><li>• Matching placebo for 28 days</li></ul> <p>Subjects have the option to return on Day 3 for vital sign. Subjects will then visit the clinic at weekly intervals (Day 7, 14 and 21) for safety, PK, and PD assessments. On visit days, subjects will be instructed to take their medications at the site. On Day 27, patients will commence a final 24 hour ABPM assessment and then return the next day to have the device removed and then begin collection of Day 28 steady-state PK and PD assessments. Patients will be asked to return after approximately 1 week for end of study (EOS) assessments.</p>
<b>Population</b>	<p>The study population will be comprised of patients with uncontrolled hypertension (here defined as having a mean daytime systolic BP <math>\geq 135</math> mmHg by ABPM) despite treatment with optimal doses of an ARB plus a diuretic plus at least one additional class of anti-hypertensive medications.</p> <p>Approximately 80 patients age 40 to 85 years old (inclusive) will be enrolled and randomized in the study.</p>
<b>Inclusion criteria</b>	<ul style="list-style-type: none"><li>• Written informed consent must be obtained before any assessment is performed.</li><li>• Male and female patients, age 40 to 85 years inclusive.</li><li>• Demonstrating a <math>\geq 80\%</math> medication compliance rate during the single-blind run-in period.</li><li>• Patients with uncontrolled hypertension (here defined as having a mean daytime systolic BP <math>\geq 135</math> mmHg by ABPM at screening) despite treatment with a stable (at least 1 month) regimen that includes an optimal dose of an ARB plus optimal doses of a diuretic plus at least one additional class of anti-hypertensive medication.</li></ul> <p>For the purposes of this trial, optimal doses of anti-hypertensive medications are defined as:</p> <ul style="list-style-type: none"><li>• the highest dose listed in the clinical practice guideline from the American Society for Hypertension and the International Society for Hypertension (<a href="#">Weber et al 2014</a>) or</li><li>• the highest allowable prescribed dose per the manufacturer's label or</li><li>• the highest dose tolerated by an individual patient or</li><li>• the highest dose appropriate for an individual patient in the judgment of the Investigator</li></ul> <p>Note: documented ABPM values within 3 months of screening are acceptable.</p> <ul style="list-style-type: none"><li>• Subjects must weigh at least 45 kg to participate in the study and must have a body mass index (BMI) within the range of 18-40 kg/m<sup>2</sup>.</li></ul>

	<ul style="list-style-type: none"> <li>• Able to communicate well with the investigator, to understand and comply with the requirements of the study.</li> </ul>
<b>Exclusion criteria</b>	<ul style="list-style-type: none"> <li>• Patients with an estimated GFR &lt;60 ml/min/1.73m<sup>2</sup>.</li> <li>• Use of angiotensin converting enzyme inhibitors (ACE-inhibitors). Note: Patients who discontinue their ACE-inhibitor and substitute with an angiotensin receptor blocker may be eligible to be re-screened provided their anti-hypertensive regimen has been stable for at least 1 month. Any substitutions or changes to a patient's anti-hypertensive regimen should be done under the guidance of the patient's treating physician.</li> <li>• Severe hypertension as defined by systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg at screening or baseline.</li> <li>• A history of secondary hypertension of any etiology including but not limited to unilateral or bilateral renal artery stenosis, polycystic kidney disease, coarctation of the aorta, primary hyperaldosteronism, Cushing's disease, pheochromocytoma, and drug-induced hypertension. If the patient has not been evaluated for secondary hypertension, investigators are responsible to evaluate all potential secondary causes of hypertension considering clinical history, physical examination, laboratory investigations or other relevant diagnostic measures in accordance with current practices and clinical guidelines before entering the patient into the study (Chobanian et al 2003; Mancia et al 2013; Weber et al 2014).</li> <li>• Known current significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or significant severe valvular disease on prior or current echocardiogram).</li> <li>• A history of known moderate or malignant hypertensive retinopathy defined as moderate (retinal signs of hemorrhage), microaneurysms, cotton-wool spots, hard exudates, or a combination thereof) or malignant (signs of moderate retinopathy plus swelling of the optic disk). Patients with a stable ophthalmologic history in the past 6 months are eligible. Any new or progressive retinal changes, acute glaucoma or other ophthalmologic conditions within the past 6 months should be evaluated by the treating ophthalmologist during screening.</li> <li>• To facilitate ABPM assessment, an upper arm circumference greater than 42 cm or third shift or overnight workers.</li> <li>• History within the previous 6 months of myocardial infarction, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), hypertensive encephalopathy, stroke, or transient ischemic attack (TIA).</li> <li>• Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.</li> </ul>
<b>Investigational and reference therapy</b>	<p>Subjects will be assigned to one of the following 3 treatment arms in a ratio of 1:1:2:</p> <p>Study treatments are defined as:</p> <ul style="list-style-type: none"> <li>• A: 100 mg LHW090</li> <li>• B: 200 mg LHW090</li> <li>• C: matching placebo</li> </ul>
<b>Efficacy/PD assessments</b>	<ul style="list-style-type: none"> <li>• ABPM</li> </ul>

<b>Safety assessments</b>	<ul style="list-style-type: none"><li>• Vital signs</li><li>• Hematology</li><li>• Chemistry</li><li>• Urinalysis</li><li>• ECG evaluation</li><li>• Physical exam</li><li>• AE/SAEs</li></ul>
<b>Other assessments</b>	Corporate Confidential Information
<b>Data analysis</b>	<p>The primary efficacy variable will be the change in the 12 hour average of systolic blood pressure measured by ambulatory blood pressure monitoring (ABPM) 28 days following the start of treatment. Out-of-office ABPM is a more reliable measure of a patient's blood pressure than office-based BP readings which may be falsely elevated because of "white-coat" phenomena (<a href="#">Bakris et al 2010</a>). The change from baseline in the placebo group will be compared to the change from baseline in the <b>pooled</b> LHW090 doses. The criteria to demonstrate efficacy (success) will be based on statistically significant (1-sided <math>p&lt;0.1</math>) greater reduction from baseline in mean daytime SBP with active treatment (pooled doses) than with placebo, as well as an estimated median reduction on active treatment (pooled active doses) of at least 7 mmHg higher than on placebo. The threshold of a 7 mmHg reduction in placebo-adjusted systolic BP by ABPM is considered clinically significant since similar magnitude changes were observed in a phase 3 trial of an endothelin-receptor antagonist, darusentan, for the same indication (<a href="#">Weber et al 2009</a>).</p> <p>Study patients will be randomized into one of 3 groups, placebo, 100 mg LHW090 and 200 mg LHW090, as an add-on therapy to conventional background anti-hypertensive therapy. 40 patients will be randomized to placebo, and 20 to each dose of active treatment. This will give around 32 completers in the placebo group and 16 on each active dose group. The primary analysis of change in mean daytime systolic blood pressure will be performed using the data collected during the period 0900 to 2100 consistent with recommendations from the European Society for Hypertension (<a href="#">O'Brien et al 2013</a>). The average of these 12 hours of data will be produced using data from the baseline ambulatory blood pressure monitoring on Day -2 and Day 27.</p> <p>The change from baseline in mean daytime SBP will be estimated from a longitudinal model using all data collected for every patient until Day 27. The model will include fixed effects for baseline, treatment (including dose), and visit, and a random effect for each subject. This analysis is unbiased under the assumption that the data are missing at random (MAR).</p>
<b>Key words</b>	Resistant hypertension

## 1 Introduction

### 1.1 Background

The adequate and timely control of blood pressure in patients diagnosed with hypertension is an important public health goal. Hypertension is a major risk factor for heart disease, kidney disease and stroke. Despite the available medications that treat high blood pressure, hypertension remains uncontrolled in more than 50% of patients (Valderrama et al 2012). The phenomenon of resistant hypertension (RHT) was defined by JNC 7 in 2003 as blood pressure that was uncontrolled despite treatment with three or more anti-hypertensive agents, one of which is a diuretic (Chobanian et al 2003). More recently, the European Society for Cardiology (ESC) and the joint American Society of Hypertension and the International Society of Hypertension (ASH/ISH) have issued similar definitions (Mancia et al 2013; Weber et al 2014). Patients with RHT are more likely to display the sequelae of uncontrolled hypertension such as an enlarged heart or kidney damage. Depending on the population examined and the level of medical screening, it has been estimated that 5 to 30% of the hypertensive population may meet this definition (James et al 2014); however, the prevalence is likely to rise with aging of the population and the increasing incidence of diabetes, obesity, and chronic kidney disease.

The natriuretic peptide (NP) family mediates a wide-ranging number of potentially salutary effects on the heart, vasculature, kidney and other target tissues. The NP family is comprised of three structurally related peptide hormones—atrial natriuretic peptide (ANP), B-type natriuretic peptide (BNP) and C-type natriuretic peptide (CNP). ANP and BNP are primarily expressed in the heart and released by cardiomyocytes in response to mechanical stretch. Binding of natriuretic peptides to their receptors, NPR-A and NPR-B, activates a guanylate cyclase resulting in increased intracellular levels of cGMP. Physiologically, NPs have been shown to stimulate the excretion of sodium and water by the kidneys, induce relaxation of vascular smooth muscle cells, and have anti-fibrotic and anti-hypertrophic effects on the heart. ANP is largely degraded by a transmembrane endopeptidase called neprilysin (NEP) while a smaller fraction is removed from the circulation by binding to a clearance receptor, NPR-C. Studies suggest that circulating levels of ANP can be increased by inhibiting NEP. Thus, NEP inhibitors are a potential therapeutic target for the treatment of hypertension. Clinically, NEP inhibitors given in combination with an angiotensin receptor blocker (ARB) have been shown to reduce blood pressure in patients with essential hypertension (Bavishi et al 2015). NEP inhibition in combination with an ARB may represent an attractive therapeutic option for patients with RHT.

LHW090 is an orally administered prodrug, which upon ester hydrolysis is metabolized to LHV527, a highly potent and specific inhibitor of NEP. LHW090 was safe and well-tolerated when administered to healthy subjects and subjects with baseline chronic renal insufficiency. The purpose of the current study is to determine whether LHW090 displays the clinical safety and efficacy profile to support further development for RHT.

**1.1.1    Relevant data summary**

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### **1.2 Study purpose**

The purpose of the present study is to determine whether LHW090 displays the clinical safety and efficacy profile to support further development in patients with resistant hypertension.

## 2 Study objectives

### 2.1 Primary objective(s)

Objective	Endpoint
<ul style="list-style-type: none"><li>To assess the safety and tolerability of LHW090 for 4 weeks on a background of conventional anti-hypertensive medications in patients with resistant hypertension.</li></ul>	<ul style="list-style-type: none"><li>Safety endpoints (adverse events, serious adverse events) up to and including end of study assessments</li></ul>
<ul style="list-style-type: none"><li>To evaluate the effect of LHW090 on placebo-adjusted mean daytime systolic blood pressure (SBP) after 4 weeks in patients with resistant hypertension.</li></ul>	<ul style="list-style-type: none"><li>Change from baseline daytime SBP on week 4 by Ambulatory blood pressure monitoring</li></ul>

### 2.2 Secondary objective(s)

Objective	Endpoint
<ul style="list-style-type: none"><li>To evaluate the pharmacokinetics (PK) of LHW090 and its active metabolite LHV527 in patients with resistant hypertension.</li></ul>	<ul style="list-style-type: none"><li>PK parameters on Day 28 (Cmax, Tmax, AUClast, AUC0-t)</li></ul>

### 2.3 Exploratory objective(s)

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### 3      Investigational plan

#### 3.1    Study design

This is a non-confirmatory, randomized, sponsor open, site and subject blind, parallel group, placebo-controlled study to evaluate the safety and efficacy of 4 weeks once daily treatment with LHW090 in patients with resistant hypertension. Patients with uncontrolled hypertension defined as a mean daytime systolic blood pressure  $\geq 135$  mmHg by ambulatory blood pressure monitoring (ABPM) on a stable (at least 1 month) regimen of optimal doses of an angiotensin receptor blocker (ARB) plus a diuretic plus at least one additional class of anti-hypertensive medication will be considered for this trial (Weber et al 2014; Vongpatanasin 2014; Calhoun et al 2008). Patients with resistant hypertension will be randomized to either placebo or 1 of 2 dose regimens of LHW090, i.e. LHW090 100 mg once daily, LHW090 200 mg once daily, as an add-on to their anti-hypertensive regimen at baseline.

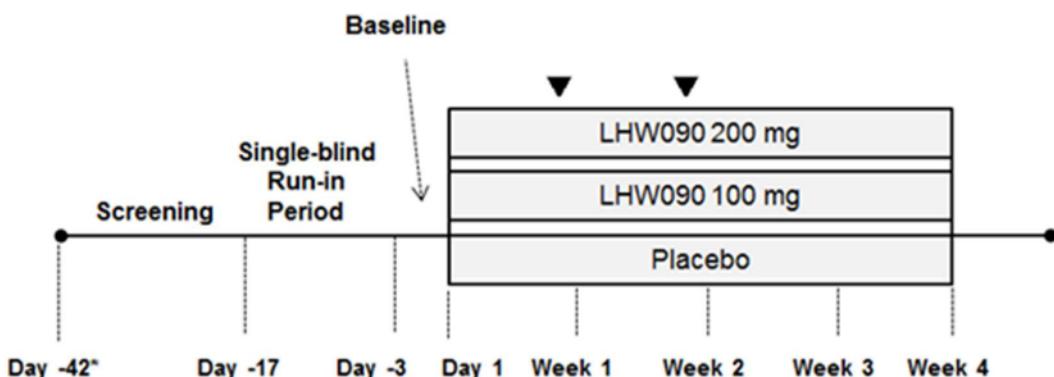
Each patient will participate in an approximately 3 week screening period, a 2-week single blind placebo run-in period, baseline assessments, a 4 week treatment period, and an end of study assessment (Figure 3-1). During the 2 week placebo run-in period, patients will receive regular reminders by the site to be compliant with their anti-hypertensive medications. At the end of this run-in period, patients who demonstrate  $\geq 80\%$  compliance with placebo will be randomized. Compliance will be established by pill count and review of medication diary. Patients will be advised that study entry cannot be fully determined until the completion of the run-in period.

On Day -2, patients will commence 24 hour ABPM monitoring and return the next day (Day -1) to have the ABPM device removed and the data collected. Patients may have additional attempts to complete a successful ABPM assessment (defined by satisfactory BP data sampling over the 24 hours and standards for device quality check) if the previous attempts are unsuccessful (O'Brien et al 2013). Upon collection of satisfactory baseline ABPM assessment, patients will then return for baseline pharmacodynamic assessments on Day -1 and then begin active treatment on Day 1. Patients will be randomized in a 1:1:2 fashion to either:

- LHW090 100 mg once daily for 28 days
- LHW090 200 mg once daily for 28 days
- Matching placebo for 28 days

Patients have the option to return on Day 3 for vital signs. Patients will then visit the clinic at weekly intervals (Day 7, 14 and 21) for safety, PK, and PD assessments. On visit days, patients will be instructed to take their medications at the site. On Day 27, patients will commence a final 24 hour ABPM assessment and then return the next day to have the device removed and then begin collection of Day 28 steady-state PK and PD assessments. As stated above, patients may have additional attempts to complete a successful ABPM assessment (defined by satisfactory BP data sampling over the 24 hours and standards for device quality check) at the Sponsor's discretion if previous attempts are unsuccessful (O'Brien et al 2013). Patients will be asked to return after approximately 1 week for end of study (EOS) assessments.

**Figure 3-1 Study design**



Approximately a total of 80 patients to be randomized in the study: Placebo (n~40), LHW090 100 mg (n~20), LHW090 200 mg (n~20)

\*Up to 25 days allowed for screening, but patient may proceed to run-in phase at any time once all screening requirements have been met

▼Interim analysis

### **3.2 Rationale of study design**

The study design addresses the primary objectives of evaluating the clinical safety and efficacy of LHW090 in patients with resistant hypertension as an add-on therapy to conventionally prescribed anti-hypertensive medications. The parallel design was chosen to allow comparison of LHW090 to placebo in a reasonable timeframe. The 2-week single-blind, placebo run-in period allows for an assessment of the patient's compliance with anti-hypertensive medications prior to entering the sponsor open, site and subject blind treatment period. The randomization ratio of 1:1:2 will provide equal sample sizes (1:1) in the comparison of the LHW090 patients versus the placebo patients. This ratio allows for the most powerful comparison. ABPM is the method of choice for measuring blood pressure changes with new anti-hypertensive drugs as it allows an assessment of the effect of the drug over a 24 hour period. Moreover, out-of-office BP measurements such as ABPM are considered a more reliable means of diagnosing and monitoring resistant hypertension since office-based BP may be confounded by 'white-coat' effects. Though both systolic and diastolic blood pressure readings will be collected over a 24 hour period, changes in the patient's daytime systolic blood pressure will be assessed as the primary objective in order to minimize differences in individual subject variation in daytime versus nighttime blood pressures.

### **3.3 Rationale of dose/regimen, duration of treatment**

The doses of LHW090 were selected based on the safety and tolerability observed in the FIH study. The administration of multiple doses of LHW090 in healthy subjects up to 400 mg once daily for 14 days was safe and well tolerated with no deaths or severe adverse events reported. Most adverse events were mild and none of the adverse events led to the discontinuation of the subjects from the study. The relationship between exposure (AUC24hr)

and urine cGMP excreted over 24 hours was analyzed in healthy subjects. Based on Emax modeling, LHW090 100 mg once daily was estimated to be the ED<sub>90</sub>. Experience with the combined angiotensin receptor-neprilysin inhibitor compound, LCZ696, across multiple studies of patients with essential hypertension, suggests that the pharmacodynamic effects on urine cGMP peak at lower doses than the peak BP lowering effects; this is the rationale for studying the 200 mg dose level. Moreover, in the LCZ696 studies, most of the antihypertensive effect of LCZ696 had occurred by the fourth week of treatment (Ruizope et al 2010). Therefore, a four week duration of treatment was selected because a shorter duration of treatment may underestimate the full antihypertensive effect of LHW090. With regard to PK, the exposure of the active metabolite LHV527 at 100 mg and 200 mg doses are expected to remain at  $\geq$  IC<sub>90</sub> levels (in vitro plasma inhibitory concentrations for NEP inhibition) across the 24 hour duration at steady-state.

### **3.4 Rationale for choice of comparator**

Not applicable.

### **3.5 Purpose and timing of interim analyses/design adaptations**

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### **3.6 Risks and benefits**

This study will be conducted in patients with resistant hypertension. There is no benefit expected for subjects participating in this study. All patients will receive study medication on top of their usual antihypertensive medications.

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There may be unknown risks of LHW090 which may be serious and unforeseen.

## **4 Population**

The study population will be comprised of patients with uncontrolled hypertension (here defined as having a daytime systolic BP  $\geq$  135 mmHg by ABPM) despite treatment with optimal doses of an ARB plus a diuretic plus at least one additional class of anti-hypertensive medication.

Approximately 80 patients, aged 40 to 85 years old (inclusive), will be enrolled and randomized in the study.

The investigator must ensure that all subjects being considered for the study meet the following eligibility criteria. No additional criteria should be applied by the investigator, in order that the study population will be representative of all eligible subjects.

Subject selection is to be established by checking through all eligibility criteria at screening and baseline (day -2). A relevant record (e.g. checklist) of the eligibility criteria must be stored with the source documentation at the study site.

Deviation from **any** entry criterion excludes a subject from enrollment into the study.

Replacement subjects will be enrolled to replace subjects who discontinue the study for reasons other than safety or lack of efficacy.

## 4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Male and female patients, age 40 to 85 years inclusive.
3. Demonstrating a  $\geq 80\%$  medication compliance rate during the single-blind run-in period.
4. Patients with uncontrolled hypertension (here defined as having a mean daytime systolic BP  $\geq 135$  mmHg by ABPM at screening) despite treatment with a stable (at least 1 month) regimen that includes optimal doses of an ARB plus a diuretic (thiazide or loop) plus at least one additional class of anti-hypertensive medication.

For the purposes of this trial, optimal doses of anti-hypertensive medications are defined as:

- the highest dose listed in the clinical practice guideline from the American Society for Hypertension and the International Society for Hypertension ([Weber et al 2014](#)) or
- the highest allowable prescribed dose per the manufacturer's label or
- the highest dose tolerated by an individual patient or
- the highest dose appropriate for an individual patient in the judgment of the Investigator

Note: documented ABPM values within 3 months of screening are acceptable.

5. Subjects must weigh at least 45 kg to participate in the study and must have a body mass index (BMI) within the range of 18-40 kg/m<sup>2</sup>.
6. Able to communicate well with the investigator, to understand and comply with the requirements of the study.

## 4.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever is longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
2. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
3. Patients with an estimated GFR  $<60$  ml/min/1.73m<sup>2</sup> at screening using the MDRD equation.
4. Use of angiotensin converting enzyme inhibitors (ACE-inhibitors).

Note: Patients who discontinue their ACE-inhibitor and substitute with an angiotensin receptor blocker may be eligible to be re-screened provided their anti-hypertensive regimen has been stable for at least 1 month. Any substitutions or changes to a patient's anti-hypertensive regimen should be done under the guidance of the patient's treating physician.

5. History of angioedema, drug-related or otherwise, as reported by the patient.

6. Clinically significant ECG abnormalities at screening as determined by the Investigator.
7. Severe hypertension as defined by an office systolic blood pressure  $\geq 180$  mmHg or diastolic blood pressure  $\geq 110$  mmHg at screening or baseline.
8. A history of secondary hypertension of any etiology including but not limited to unilateral or bilateral renal artery stenosis, polycystic kidney disease, coarctation of the aorta, primary hyperaldosteronism, Cushing's disease, pheochromocytoma, and drug-induced hypertension. If the patient has not been evaluated for secondary hypertension, investigators are responsible to evaluate all potential secondary causes of hypertension considering clinical history, physical examination, laboratory investigations or other relevant diagnostic measures in accordance with current practices and clinical guidelines before entering the patient into the study ([Chobanian et al 2003](#); [Mancia et al 2013](#); [Weber et al 2014](#)).
9. Known current significant left ventricular outflow obstruction, such as obstructive hypertrophic cardiomyopathy or significant severe valvular disease on prior or current echocardiogram).
10. A history of known moderate or malignant hypertensive retinopathy defined as moderate (retinal signs of hemorrhage), microaneurysms, cotton-wool spots, hard exudates, or a combination thereof) or malignant (signs of moderate retinopathy plus swelling of the optic disk). Patients with a stable ophthalmologic history in the past 6 months are eligible. Any new or progressive retinal changes, acute glaucoma or other ophthalmologic conditions within the past 6 months should be evaluated by the treating ophthalmologist during screening.
11. To facilitate ABPM assessment of daytime readings, an upper arm circumference greater than 42 cm or third shift or overnight workers.
12. History within the previous 6 months of myocardial infarction, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), hypertensive encephalopathy, stroke, or transient ischemic attack (TIA).
13. Hemoglobin levels below 9.0 g/dL at screening.
14. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin or *in-situ* cervical cancer), treated or untreated, within the past 1 year, regardless of whether there is evidence of local recurrence or metastases.
15. Donation or loss of 400 mL or more of blood within 8 weeks prior to initial dosing, or longer if required by local regulation.
16. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
17. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant.  
Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms), total hysterectomy or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of

the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

18. Sexually active males must use a condom during intercourse while taking drug and for 1 week after stopping study medication and should not father a child in this period. A condom is required to be used also by vasectomized men in order to prevent delivery of the drug via seminal fluid.
19. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
20. On the Columbia-Suicide Severity Rating Scale, score “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS, if this ideation occurred in the past 6 months, or “yes” on any item of the Suicidal Behavior section, except for the “Non-Suicidal-Self Injurious Behavior” (question also included in the Suicidal Behavior section), if this behavior occurred in the past 2 years. Any patient meeting this exclusion criterion should be referred to a mental health care professional.
21. Vulnerable subjects, e.g. subjects kept in detention, soldiers and employees of the sponsor or a clinical research organization, involved in this study.

Note: In the case where a safety laboratory assessment at screening and initial baseline is outside of the range specified above, the assessment may be repeated once prior to randomization. If the repeat value remains outside of the specified ranges, the subject is excluded from the study.

No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

## **5      Restrictions for Study Subjects**

Patients must be informed and reminded of the following restrictions from screening until the end of the study visit:

### **5.1     Contraception requirements**

Not applicable. Only women of non-childbearing potential will be included in this study.

### **5.2     Allowable Medications**

Allowable anti-hypertensives (besides an ARB and a diuretic) include

- Calcium channel blockers
- Beta-blockers
- Potassium-sparing diuretics such as spironolactone, eplerenone, or amiloride
- Direct vasodilators
- Alpha-blockers

Patients must be on a stable regimen throughout the trial, and for at least one month prior to the study.

### 5.3 Prohibited treatment

Use of the following medications is not allowed during the course of the study from screening (Visit 1) to the end of the study. Subjects who are receiving such medication(s) will be excluded, or if ethically and clinically justified, the medication(s) should be gradually withdrawn before Visit 2:

1. Any drug that, in the discretion of the investigator, may affect the assessment of blood pressure in this study or contribute to drug-induced hypertension such as:
  - Any anti-depressant drugs in the MAO inhibitor class, tricyclics, and venlafaxine, duloxetine, and bupropion. Other psychotropic drugs such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) are permitted if the patient has been on a stable dose for the previous 3 months.
  - Chronic administration (defined as > 3 days per week) of sympathomimetic drugs such as those found in nasal decongestants, oral decongestants, diet aids and bronchodilators. Doses of sympathomimetic drugs used occasionally are prohibited 24 hours prior to the study visit.
  - Thyroid medication, estrogen-based and/or androgen-based hormone replacement therapies unless on a stable regimen for at least 3 months prior to Visit 1 and is not expected to change during the course of the study.
  - Ergot and serotonin (5-hydroxytryptamine) receptor agonist preparations.
  - Drugs for the treatment of attention deficit hyperactivity disorder (ADHD), including methylphenidate, amphetamine, and atomoxetine.
  - Chronic administration (defined as > 3 days per week) of NSAIDs or COX-2 inhibitors. The long-term chronic use of aspirin for cardiovascular prophylaxis is allowed provided the total daily dose does not exceed 325 mg.
  - Oral nitrates. Intermittent use of sublingual nitrates are allowed but must not be used within 12 hours prior to any scheduled visit.
  - Chronic administration (defined as > 3 days per week) of PDE5 inhibitors (e.g. sildenafil, vardenafil, tadalafil). Intermittent use of PDE5 inhibitors are allowed but must not be used within 48 hours prior to any scheduled visit.
  - Chronic (defined as > 3 days per week) treatment with oral or parenteral corticosteroid treatment. The use of inhalational corticosteroids is permitted.
2. The following medications are prohibited due to potential for pharmacokinetic drug-drug interactions: amodiaquine, atazanavir, bosentan, bupropion, celecoxib, cimetidine, cyclosporine, diclofenac, efavirenz, eltrombopag, gemfibrozil, glyburide, glimepiride, imatinib, irinotecan, ifosfamide, lapatinib, lopinavir, methotrexate, mitoxantrone, paclitaxel, phenytoin, pioglitazone, probenecid, repaglinide, rifampin, ritonavir, saquinavir, tipranavir, topotecan, and warfarin.
3. All other prior non-study medications (not specifically contraindicated in the exclusion criteria will be allowed, provided the patient has been on a standard treatment regimen (at least 4 weeks of the same dose) and the treatment is not planned to be changed during the course of the study.

## 5.4 Dietary restrictions and smoking

Patients should maintain their usual diet prior to, and during the study. Alterations in diet can lead to changes in sodium and potassium intake which could influence the results of this study.

- No alcohol will be allowed starting 24 hours prior to and during study visits and ABPM assessments.
- Intake of xanthine (e.g. caffeine) containing food or beverages will be allowed during the study. Patients should be instructed to maintain their normal daily routine. However, the morning of clinic visits, patients should avoid coffee (and other caffeine containing food or beverages), smoking and exercise for at least 30 minutes prior to office BP measurements.
- In order to avoid wide variations in urine volumes on collection days, subjects should be encouraged to have a fluid intake of approximately 240 mL every 4 hours during their waking hours, in addition to the fluid taken with meals and medication.

## 5.5 General restrictions

- While wearing the ABPM, patients should avoid strenuous exercise or activity and bathing during the 24 hour period.

# 6 Treatment

## 6.1 Study treatment

Details on the storage and management of study medication, randomization and instructions for prescribing and taking study treatment are outlined in the Site Operations Manual.

### 6.1.1 Investigational treatment

The investigational drug, LHW090 100 mg and matching placebo will be prepared by Novartis and supplied to the Investigator site as single blinded patient packs.

## 6.2 Treatment arms

Patients will be assigned to one of the following 3 treatment arms in a ratio of 1:1:2:

Study treatments are defined as:

- A: 100 mg LHW090
- B: 200 mg LHW090
- C: matching placebo

## 6.3 Permitted dose adjustments and interruptions of study treatment

Study drug dose adjustments and/or interruptions are not permitted. If a short treatment interruption becomes necessary for an important reason, the subject may resume the study treatment. However, drug interruption should end at least 3 days prior to the next study visit. In any case, the compliance of the subjects will be monitored and recorded.

In the event that a subject will be transitioned to an ACE inhibitor at the end of the study or after premature discontinuation of study medication, a minimum of 48 hours must transpire between the last dose of LHW090 and the first dose of an ACE inhibitor. Consideration should also be given to the existing ARB treatment of subjects in the study; concomitant treatment with an ACE inhibitor and an ARB should be avoided according to current hypertension guidelines (James et al 2014; Mancia et al 2013; Weber et al 2014) and in compliance with applicable local prescribing information for renin angiotensin aldosterone (RAAS) agents.

## **6.4 Treatment assignment**

Randomization numbers will be assigned in ascending, sequential order to eligible patients (see Site Operations Manual for details). The investigator will enter the randomization number on the CRF.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff. A patient randomization list will be produced by the Interactive Response Technology (IRT) provider using a validated system that automates the random assignment of patient numbers to randomization numbers. These randomization numbers are linked to the different treatment arms. The randomization scheme for patients will be reviewed and approved by a member of the Novartis IIS Randomization Group.

Prior to dosing, patients who fulfill all inclusion/exclusion criteria will be randomized via IRT to one of the treatment arms. The investigator or his/her delegate will call or log on to the IRT and confirm that the patient fulfills all the inclusion/exclusion criteria. The IRT will then assign a randomization number to the patient, which will be used to link the patient to a treatment arm.

## **6.5 Treatment blinding**

This is a sponsor open, site and subject double blind study: subjects, investigator staff and persons performing the assessments will remain blind to the identity of study treatments according to the specifications provided in the Site Operations Manual. During the placebo run-in period (V2), placebo treatment will be administered to all patients and will be known by investigator staff and persons performing the assessments.

The identity of the treatments will be concealed by the use of study drugs that are all identical in packaging, labeling, schedule of administration, appearance, and odor.

Randomization data are kept strictly confidential, and are accessible only to authorized personnel, until unblinding of the trial as described in the table in the Blinding levels table in the Site Operations Manual.

The results of the interim analyses may be communicated (e.g. dose escalation decision, evaluation of PoC criteria or information needed for planning/modifying another study) to relevant Novartis teams for information, consulting and/or decision purposes.

Unblinding will only occur in the case of patient emergencies (see [Section 6.6](#)) and at the conclusion of the study.

## **6.6 Emergency breaking of assigned treatment code**

Emergency unblinding should only be undertaken when it is essential to treat the patient safely and efficaciously. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study patient who presents with an emergency condition. Emergency code breaks are performed using the IRT system. When the investigator contacts the system to unblind a patient, he/she must provide the requested patient identifying information and confirm the necessity to unblind the patient. The investigator will then receive details of the drug treatment for the specified patient and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site, the Clinical Trial Leader and Translational Medical Expert that the code has been broken. It is the investigator's responsibility to ensure that there is a procedure in place to allow access to the IRT in case of emergency. If appropriate, the investigator will inform the patient how to contact his/her backup in cases of emergency when he/she is unavailable.

An assessment will be done by the appropriate site personnel and the sponsor after an emergency unblinding to assess whether or not study drug should be discontinued for a given patient and, if applicable, whether the patient can continue into the next trial phase (e.g, an unblinded extension).

## **6.7 Treatment exposure and compliance**

Pharmacokinetic parameters (measures of treatment exposure) will be determined in all subjects treated with LHW090 as detailed in [Section 8.5](#).

## **6.8 Recommended treatment of adverse events**

Adverse events should be treated at the discretion of the Investigator based on his/her judgment and best medical practices. Medication used to treat AEs must be recorded on the Concomitant medications/Significant non-drug therapies CRF.

## **6.9 Rescue medication**

Rescue medication to treat severe or serious conditions as per standard of care, at the discretion of the Investigator, is allowed. Use of rescue medication must be recorded on the Concomitant medications/Significant non-drug therapies CRF after start of study drug.

## **6.10 Concomitant treatment**

All prescription medications, over-the-counter drugs and significant non-drug therapies (including physical therapy and blood transfusions) administered or taken within the timeframe defined in the entry criteria prior to the start of the study and during the study, must be recorded on the Concomitant medications/ Significant non-drug therapies section of the CRF.

Medication entries should be specific to trade name, the single dose and unit, the frequency and route of administration, the start and discontinuation date and the reason for therapy.

Due to the potential for pharmacokinetic drug-drug interactions, patients taking statins should be monitored for statin-related myositis (e.g. muscle pain or elevations in creatine kinase) during the duration of the study. Under the guidance of their treating physician, subjects on rosuvastatin may consider halving their dose or switching to another statin for the duration of the study.

## 7 Discontinuation and study completion

### 7.1 Discontinuation of study treatment

Subjects may voluntarily discontinue study treatment for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason. If a subject withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a subject's withdrawal from the study and record this information on the CRF.

The investigator must discontinue study treatment for a given patient if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment **must** be discontinued under the following circumstances:

- Subject withdraws consent
- Pregnancy

Discontinuation of investigational treatment will be at the discretion of the Investigator, under the following circumstances:

- Emergence of the following adverse events:
  - Symptomatic hypotension or orthostatic hypotension (hypotensive or orthostatic blood pressure readings must be confirmed on repeat measurement within 30 minutes) that requires medical intervention.
  - Systolic blood pressure <80 mm Hg (must be confirmed on repeat measurement after 30 minutes)
  - Symptomatic severe hypertension (e.g., a systolic blood pressure >180 mmHg or a diastolic blood pressure >120 mmHg) that requires medical intervention
- Any of the following laboratory abnormalities:
  - A reproducible and persistent (> 24 hours) increase in serum creatinine from baseline of >0.3 mg/dL unless the benefit/risk assessment supports continuing study treatment. A renal event leading to patient discontinuation should be followed up until event resolution (Serum Cr within 10% of baseline), or event stabilization (Serum Cr level with  $\pm 10\%$  variability over last 6 months).
- Use of prohibited treatment as per [Section 5.3](#)
- Any other protocol deviation that results in a significant risk to the subject's safety

The appropriate personnel from the site and Novartis will assess whether investigational treatment should be discontinued for any subject whose treatment code has been broken inadvertently for any reason.

Subjects who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see [Section 7.3](#)). Where possible, they should return for the assessments outlined at V777 in the assessment table. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact them as specified in [Section 7.2.1](#)

## **7.2 Study completion and post-study treatment**

Each subject will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them. Study completion is defined as when the last subject completes their End of Study visit, and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator, or in the event of an early study termination decision, the date of that decision.

At a minimum, subjects will be contacted for safety evaluations during the 30 days following the Study Completion visit, including a final post-study safety contact at the 30-day point. Documentation of attempts to contact the subject should be recorded in the source documentation.

### **7.2.1 Lost to follow-up**

For subjects whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator should show "due diligence" by documenting in the source documents steps taken to contact the subject, e.g. dates of telephone calls, registered letters, etc. A subject should not be formally considered lost to follow-up until his/her scheduled end of study visit would have occurred.

## **7.3 Withdrawal of consent**

Patients may voluntarily withdraw consent to participate in the study for any reason at any time.

Withdrawal of consent occurs only when a patient does not want to participate in the study anymore **and** does not want any further visits or assessments **and** does not want any further study related contact **and** does not allow analysis of already obtained biologic material.

If a patient withdraws consent, the investigator must make every effort to determine the primary reason for this decision and record this information. Study treatment must be discontinued and no further assessments conducted. All biological material that has not been analyzed at the time of withdrawal must not be used. Further attempts to contact the patient are not allowed unless safety findings require communicating or follow-up.

## **7.4 Study Stopping rules**

The study will be stopped if any of the following criteria are met and no further dosing will be taken pending a full safety review:

- 2 severe AEs are reported
- 3 subjects experience a persistent (> 24 hours) and reproducible increase in serum creatinine >0.3 mg/dL from baseline
- 3 or more subjects experience a similar AE which is assessed as either moderate or severe in intensity

## **7.5 Early study termination**

The study can be terminated at any time for any reason by Novartis. Should this be necessary, subjects should be seen as soon as possible and treated as a prematurely withdrawn subject. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the subject's interests.

The investigator will be responsible for informing IRBs/IECs of the early termination of the trial.

## 8 Procedures and assessments

**Table 8-1 Assessment schedule**

Subjects should be seen for all visits on the designated day, with the assessments performed as per schedule, within the allowed “visit/assessment window” specified in the Site Operations Manual.

Study Phase	Screening	PBO Run In	Baseline				Treatment							Study Completion							
			V1	V2 <sup>12</sup>	V3 <sup>13</sup>	V4	V5	V6 <sup>19</sup>	V7	V8	V9	V10	V11								
Visit Numbers <sup>1</sup>	V1	V2 <sup>12</sup>	-17 to -3	-2	-1		1	3	7	14	21	27		28		35					
Study Day(s)	-42 to -18	(-2, +1)	(-2, 0)	(-2, 0)				(-1, +1)	(-1, +1)	(-1, +2)	(-1, +1)	(-2, +1)		(-1, +1)		(-2, +2)					
Time (post-dose)	-	-	-	0h	4h <sup>4</sup>	8h <sup>4</sup>	12h <sup>5</sup>	0h	-	-	-	-	-	0h	1h	2h	3h	4h <sup>4</sup>	8h <sup>4</sup>	12h <sup>6</sup>	-
Informed consent	X																				
Inclusion / Exclusion criteria <sup>7</sup>	X			X																	
Medical history/current medical conditions	X																				
Demography	X																				
Hepatitis and HIV Screen <sup>7</sup>	X																				
Blood pressure / Pulse rate <sup>8</sup>	X	X	X	X				X	X	X	X	X	X				X				
Body temperature	X		X	X																	
Body Height and Weight	X																				
Ambulatory blood pressure monitoring <sup>9</sup> <sup>17</sup>	X <sup>8</sup>		X										X <sup>14</sup>		X <sup>14</sup>						
Physical examination <sup>7</sup>	X	X						X					X		X				X		
Alcohol Test, Drug Screen, and Cotinine Test <sup>7</sup>	X																				
ECG evaluation	X												X								
Routine Clinical Laboratory Tests <sup>12</sup>	X		X										X	X	X				X		
Urinalysis	X		X										X	X	X				X		
Suicidality Assessment with C-SSRS	X		X										X			X			X		
IVRS <sup>15</sup>	X					X															
Patient diary <sup>16</sup>		X	X										X								
Dose administration		X	X		X								X								
Concomitant therapies													as required						as required		
Adverse events													as required						as required		
Serious adverse events													as required						as required		
Comments													as required						as required		
Corporate Confidential Information				X									X	X	X	X	X	X			
				X	X	X	X	X					X			X	X	X			
				X	X	X										X		X			
					X		X									X					
Study completion information																		X			

<sup>1</sup>Visit structure given for internal programming purpose only

## Corporate Confidential Information

Urine pooling periods are 0-4 hr and 4-8 hr.

<sup>5</sup>Day-1, 12 h PD blood collection is optional

<sup>6</sup>Day 28, 12 h PK and PD collection is optional

<sup>7</sup>Captured in source documentation only

<sup>8</sup>Standing and sitting vitals will be taken at screening; on subsequent visits, readings will be taken in a sitting position (standing may be performed if necessary at Investigator discretion)

<sup>9</sup>Documented ABPM values within 3 months of screening is acceptable for inclusion into the trial

## Corporate Confidential Information

<sup>12</sup>Routine clinical laboratory tests includes hematology, clinical chemistry (+ lipid profile), and NTproBNP

<sup>14</sup>ABPM assessments during the treatment period must be recorded by unblinded site personnel

<sup>15</sup>IVRS must be used to register a patient at screening, and to randomize a patient prior to the first dose once eligibility is confirmed

<sup>16</sup>Patient diary will be reviewed at V3 (to assess adherence to medication regimen during the PBO run-in), and at every visit during the treatment period

<sup>17</sup>ABPM readings will be obtained over a 24 h period. Patients must return to the site after 24 h to have the device removed and results transmitted by site personnel.

<sup>18</sup>Visitwindows allow V3 to overlap with V2 and V4; note that no visits can be combined together

<sup>19</sup>Visit is optional

## **8.1 Informed consent procedures**

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

Informed consent must be obtained before conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the subject source documents.

The date of signing of informed consent (and withdrawal, if later withdrawn) should be documented in the CRF.

Novartis will provide to investigators a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC.

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

### **Corporate Confidential Information**

In the event that Novartis wants to perform testing on the samples that are not described in this protocol, additional Institutional Review Board and/or Ethics Committee approval will be obtained.

A copy of the approved version of all consent forms must be provided to the Novartis monitor after IRB/IEC approval.

## **8.2 Subject demographics/other baseline characteristics**

Subject demographic and baseline characteristic data will be collected on all subjects.

Relevant medical history/current medical conditions data includes data until signature of informed consent. Where possible, diagnoses and not symptoms will be recorded.

Investigators have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

## 8.3 Efficacy / Pharmacodynamics

Pharmacodynamic assessments are specified below, with the methods for assessment and recording specified in the Study Operations Manual. Assessments will be performed/samples collected at the timepoint(s) defined in the [Assessment schedule](#).

In order to better define the PD profile, the timing of the sample collection may be altered based on emergent data. The number of samples/blood draws and total blood volume collected will not exceed those stated in the protocol. The results need to remain blinded during the study.

### 8.3.1 Ambulatory blood pressure monitoring

Continuous blood pressure monitoring will be performed over 24 hour periods to assess blood pressure, heart rate, mean arterial pressure, and pulse pressure.

The ABPM device vendor will provide a reference/user manual giving more specific details on patient considerations for inclusion. Procedures for set-up, validation, quality control, use of software and transfer of data, and guidance for performing the measurements will also be provided in the vendor manual. Investigator site staff that will be performing the ABPM measurements will be trained appropriately by the device vendor to ensure the devices are used in the correct manner. Training will occur prior to initial use of the devices.

## 8.4 Safety

Safety assessments are specified below; methods for assessment and recording are specified in the Site Operations Manual, with the [Assessment schedule](#) detailing when each assessment is to be performed.

### 8.4.1 Physical examination

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and/or pelvic exams may be performed.

Information for all physical examinations should be included in the source documents and will not be transferred to the sponsor as part of the study analysis. Significant findings that are present prior to informed consent are included in the Relevant Medical History section of the source documents. Significant findings observed after informed consent signature which meet the definition of an Adverse Event must be appropriately recorded on the Adverse Event eCRF section.

### 8.4.2 Vital signs

- Body temperature
- Blood pressure (BP)
- Pulse

#### **8.4.3 Height and weight**

- Height
- Body weight
- Body mass index (BMI) will be calculated (Body weight (kg) / [Height (m)]<sup>2</sup>)

#### **8.4.4 Laboratory evaluations**

Clinically relevant deviations of laboratory test results occurring during or at completion of the study must be reported and discussed with Novartis personnel. The results should be evaluated for criteria defining an adverse event and reported as such if the criteria are met. Repeated evaluations are mandatory until normalization of the result(s) or until the change is no longer clinically relevant. In case of doubt, Novartis personnel should again be contacted.

#### **Hematology**

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential and platelet count will be measured.

#### **Clinical chemistry**

Sodium, potassium, creatinine, urea, uric acid, chloride, albumin, calcium, alkaline phosphatase, total bilirubin, LDH, GGT, AST, ALT, glucose, total cholesterol, creatine kinase (CK), and triglycerides.

If the total bilirubin concentration is increased above 1.5 times the upper limit of normal, direct and indirect reacting bilirubin should be differentiated.

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#### **Urinalysis**

Urine test by dipstick e.g. Combur9: leucocytes, nitrite, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood/ hemoglobin

If the dipstick result is positive for protein, nitrite, leucocytes and/or blood, the sample will be sent for microscopic analysis of WBC, RBC and casts.

#### **8.4.5 Electrocardiogram (ECG)**

Each ECG tracing should be labeled with study number, subject initials, subject number, date and time, be appropriately signed and dated to confirm review and filed in the study site source documents. For any ECGs with subject safety concerns, two additional ECGs should be performed to confirm the safety finding. Clinically significant ECG findings prior to dosing with investigational treatment must be discussed with the sponsor.

Full details of all procedures relating to the ECG collection and reporting will be contained in the technical manual which is provided to the site by the core laboratory.

**For all studies:**

PR interval, QRS duration, heart rate, RR, QT, QTc

The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

**8.5 Pharmacokinetics**

PK samples will be collected at the time-points defined in the [Assessment schedule](#).

Further details on sample collection, numbering, processing and shipment can be found in the Site Operations Manual.

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For standard pharmacokinetic abbreviations and definitions see the list provided at the beginning of this protocol.

The following pharmacokinetic parameters will be determined using the actual recorded sampling times and non-compartmental method(s) with Phoenix WinNonlin (Version 6.2 or higher): Cmax, Tmax, AUClast, AUC0-t from the plasma concentration-time data. Other pharmacokinetic parameters may be determined, if relevant.

**8.6 Other assessments**

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## **9 Safety monitoring**

### **9.1 Adverse events**

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the subject at each visit during the study. Adverse events also may be detected when they are volunteered by the subject during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patients with underlying disease. Investigators have the responsibility for managing the safety of individual subject and identifying adverse events. Alert ranges for liver related events are included in [Section 9.3](#).

Adverse events must be recorded on the Adverse Events CRF for subjects that pass screening and enter into the study. The adverse events should be reported according to the signs, symptoms or diagnosis associated with them, and accompanied by the following information:

1. the severity grade
  - mild: usually transient in nature and generally not interfering with normal activities
  - moderate: sufficiently discomforting to interfere with normal activities
  - severe: prevents normal activities
2. its relationship to the investigational treatment (no/yes), or other study treatment (non-investigational) (no/yes), or both or indistinguishable,
3. its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
4. whether it constitutes a serious adverse event (SAE). See [Section 9.2](#) for definition of SAE
5. action taken regarding [study/investigational] treatment(select as appropriate).

All adverse events should be treated appropriately. Treatment may include one or more of the following:

- no action taken (i.e. further observation only)
- study treatment dosage adjusted/temporarily interrupted
- study treatment permanently discontinued due to this adverse event
- concomitant medication given
- non-drug therapy given
- subject hospitalized/subject's hospitalization prolonged

6. its outcome (continuing at final exam; resolved)

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or Core Data Sheet (for marketed drugs) or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the subject informed consent and should be discussed with the subject during the study as needed.

The investigator should also instruct each subject to report any new adverse event (beyond the protocol observation period) that the subject, or the subject's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

## **9.2 Serious adverse event reporting**

### **9.2.1 Definition of SAE**

An SAE is defined as any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria:

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
  - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
  - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
  - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the subject or may require medical or surgical intervention.

Life-threatening in the context of a SAE refers to a reaction in which the subject was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

All malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization or development of dependency or abuse.

All AEs (serious and non-serious) are captured on the CRF, SAEs also require individual reporting to DS&E as per [Section 9.2.2](#).

### **9.2.2 SAE reporting**

To ensure subject safety, every SAE, regardless of causality, occurring after the subject has provided informed consent and until 30 days after the last study visit must be reported to Novartis within 24 hours of learning of its occurrence as described below. Any SAEs experienced after this should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

SAEs (initial and follow-up) that are recorded electronically in the Electronic Data Capture system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first. Study site personnel must also inform the Clinical Trial Leader.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the subject continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the investigational treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same investigational treatment that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

### **9.3 Liver safety monitoring**

To ensure subject safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

The following two categories of abnormalities / adverse events have to be considered during the course of the study:

- Liver laboratory triggers, which will require repeated assessments of the abnormal laboratory parameter
- Liver events, which will require close observation, follow-up monitoring and completion of the standard base liver CRF pages

Please refer to [Table 9-1](#) and [Table 9-2](#) for complete definitions of liver laboratory triggers and liver events.

Every liver laboratory trigger or liver event should be followed up by the investigator or designated personal at the trial site, as summarized below and detailed in [Table 9-2](#).

#### **For the liver laboratory trigger:**

- Repeating the LFT within the next week to confirm elevation.

These LFT repeats should be performed using the central laboratory if possible. If this is not possible, then the repeats can be performed at a local laboratory to monitor the safety of the patient. Repeats laboratory should then be performed at central laboratory as soon as possible. If a liver event is subsequently reported, any local LFTs previously conducted that are associated with this event should be reported on the Liver CRF pages.

#### **For the liver events:**

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug (refer to [Section 7.1](#), if appropriate)
- Hospitalization of the subject if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g. disease, co-medications)
- An investigation of the liver event which needs to be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded as appropriate in the CRF, including the liver event overview CRF pages.

**Table 9-1 Liver Event and Laboratory Trigger Definitions**

Definition/ threshold	
Liver laboratory triggers	<ul style="list-style-type: none"> <li>• <math>3 \times \text{ULN} &lt; \text{ALT} / \text{AST} \leq 5 \times \text{ULN}</math></li> <li>• <math>1.5 \times \text{ULN} &lt; \text{TBL} \leq 2 \times \text{ULN}</math></li> </ul>
Liver events	<ul style="list-style-type: none"> <li>• <math>\text{ALT or AST} &gt; 5 \times \text{ULN}</math></li> <li>• <math>\text{ALP} &gt; 2 \times \text{ULN}</math> (in the absence of known bone pathology)</li> <li>• <math>\text{TBL} &gt; 2 \times \text{ULN}</math> (in the absence of known Gilbert syndrome)</li> <li>• <math>\text{ALT or AST} &gt; 3 \times \text{ULN}</math> and <math>\text{INR} &gt; 1.5</math></li> <li>• Potential Hy's Law cases (defined as <math>\text{ALT or AST} &gt; 3 \times \text{ULN}</math> and <math>\text{TBL} &gt; 2 \times \text{ULN}</math> [mainly conjugated fraction] without notable increase in <math>\text{ALP}</math> to <math>&gt; 2 \times \text{ULN}</math>)</li> <li>• Any clinical event of jaundice (or equivalent term)</li> <li>• <math>\text{ALT or AST} &gt; 3 \times \text{ULN}</math> accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia</li> <li>• Any adverse event potentially indicative of a liver toxicity *</li> </ul>

**Table 9-2 Follow Up Requirements for Liver Events and Laboratory Triggers**

Criteria	Actions required	Follow-up monitoring
Potential Hy's Law case <sup>a</sup>	<ul style="list-style-type: none"> <li>• Discontinue the study drug immediately</li> <li>• Hospitalize, if clinically appropriate</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
ALT or AST		
$> 8 \times \text{ULN}$	<ul style="list-style-type: none"> <li>• Discontinue the study drug immediately</li> <li>• Hospitalize if clinically appropriate</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
$> 3 \times \text{ULN}$ and $\text{INR} > 1.5$	<ul style="list-style-type: none"> <li>• Discontinue the study drug immediately</li> <li>• Hospitalize, if clinically appropriate</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)
$> 5$ to $\leq 8 \times \text{ULN}$	<ul style="list-style-type: none"> <li>• Repeat LFT within 48 hours</li> <li>• If elevation persists, continue follow-up monitoring</li> <li>• If elevation persists for <i>more than 2 weeks</i>, discontinue the study drug</li> <li>• Establish causality</li> <li>• Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and $\gamma$ GT until resolution <sup>c</sup> (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
> 3 × ULN accompanied by symptoms <sup>b</sup>	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
> 3 to ≤ 5 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks
ALP (isolated)		
> 2 × ULN (in the absence of known bone pathology)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
TBL (isolated)		
> 2 × ULN (in the absence of known Gilbert syndrome)	<ul style="list-style-type: none"> <li>Repeat LFT within 48 hours</li> <li>If elevation persists, discontinue the study drug immediately</li> <li>Hospitalize if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 2 × ULN (patient is asymptomatic)	<ul style="list-style-type: none"> <li>Repeat LFT within the next week</li> <li>If elevation is confirmed, initiate close observation of the patient</li> </ul>	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
Jaundice	<ul style="list-style-type: none"> <li>Discontinue the study drug immediately</li> <li>Hospitalize the patient</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	ALT, AST, TBL, Alb, PT/INR, ALP and γGT until resolution <sup>c</sup> (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	<ul style="list-style-type: none"> <li>Consider study drug interruption or discontinuation</li> <li>Hospitalization if clinically appropriate</li> <li>Establish causality</li> <li>Complete liver CRF</li> </ul>	Investigator discretion

\*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

<sup>a</sup>Elevated ALT/AST > 3 × ULN and TBL > 2 × ULN but without notable increase in ALP to > 2 × ULN

<sup>b</sup>(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia

<sup>c</sup>Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

## 9.4 Renal safety monitoring

Renal events are defined as one of the following:

- confirmed (after  $\geq 24\text{h}$ ) increase in serum creatinine of  $\geq 25\%$  compared to baseline during normal hydration status
- new onset ( $\geq 1+$ ) proteinuria, hematuria or glucosuria; or as a
- doubling in the urinary albumin-creatinine ratio (ACR) or urinary protein-creatinine ratio (PCR) (if applicable).

The following two categories of abnormalities/adverse events have to be considered during the course of the study:

- Serum creatinine triggers that will require follow up and repeat assessments of the abnormal laboratory parameter
- Urine dipstick triggers that will require follow up and repeat assessments of the abnormal laboratory parameter

**Table 9-3 Specific Renal Alert Criteria and Actions**

Renal Event	Actions
Serum creatinine increase 25 – 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Serum creatinine increase $\geq 50\%$ compared to baseline	Follow up within 24-48h if possible Consider drug interruption Consider patient hospitalization /specialized treatment
Albumin- or Protein-creatinine ratio increase $\geq 2$ -fold	Confirm value after 24-48h Perform urine microscopy
Albumin-creatinine ratio (ACR) $\geq 30\text{ mg/g}$ or $\geq 3\text{ mg/mmol}$ ;	Consider drug interruption / discontinuation
New dipstick proteinuria $\geq 1+$ Protein-creatinine ratio (PCR) $\geq 150\text{ mg/g}$ or $>15\text{ mg/mmol}$	
New dipstick glucosuria $\geq 1+$ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
Document contributing factors: co-medication, other co-morbid conditions, and additional diagnostic procedures performed in the CRF	
<u>Monitor patient regularly (frequency at investigator's discretion) until one of the following:</u>	
Event resolution: (sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline)	
Event stabilization: sCr level with $\pm 10\%$ variability over last 6 months or protein-creatinine ratio stabilization at a new level with $\pm 50\%$ variability over last 6 months.	

## **9.5      Pregnancy reporting**

Pregnancy outcomes must be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

## **9.6      Prospective suicidality assessment**

The Columbia-Suicide Severity Rating Scale (C-SSRS), is a questionnaire that prospectively assesses Suicidal Ideation and Suicidal Behavior.

The C-SSRS, which uses a semi-structured interview to probe subject responses, will be administered by an individual who has received training and certification in its administration. At screening and baseline visits, the “baseline/screening” version of the C-SSRS, will be administered. This version assesses Suicidal Ideation and Suicidal Behavior during the subject’s lifetime and during a predefined period. At subsequent visits, the “since last visit” version will be administered.

If, at any time after screening and/or baseline, the score is “yes” on item 4 or item 5 of the Suicidal Ideation section of the C-SSRS or “yes” on any item of the Suicidal Behavior section, the subject **must** be referred to a mental health care professional for further assessment and/or treatment. The decision on whether the study treatment should be discontinued is to be taken by the investigator in consultation with the mental health professional to whom the subject is referred.

In addition, all life-threatening events should be reported as SAEs. For example, if a subject answers “yes” to one of the questions in the Suicidal Behavior section, an SAE must be reported if the event was life-threatening. All events of “Non-Suicidal Self-Injurious Behavior” (question also included in the Suicidal Behavior section) should be reported as AEs and assigned the appropriate severity grade.

All SAEs relating to suicidal behavior should be reviewed by the Safety Management Team or Early Project Teams.

## **9.7      Early phase safety monitoring**

The Investigator will monitor adverse events in an ongoing manner and inform the Sponsor of any clinically relevant observations. Any required safety reviews will be made jointly between medically qualified personnel representing the Sponsor and Investigator. Such evaluations may occur verbally, but the outcome and key discussion points will be summarized in writing (e-mail) and made available to both Sponsor and all Investigator(s). Criteria pertaining to stopping the study/treatment or adapting the study design are presented above.

When two or more clinical site(s) are participating in the clinical study, the Sponsor will advise the Investigator(s) at all sites in writing (e-mail) (and by telephone if possible) of any new, clinically relevant safety information reported from another site during the conduct of the study in a timely manner.

## **10 Data review and database management**

### **10.1 Site monitoring**

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The monitor will visit the site to check the completeness of subject records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the monitor during these visits.

The investigator must maintain source documents for each subject in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the subject's file. The investigator must also keep the original informed consent form signed by the subject (a signed copy is given to the subject).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the eligibility criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

### **10.2 Data collection**

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies and, by generating appropriate error messages, allow the data to be confirmed or corrected before transfer of the data to the CRO working on behalf of Novartis. The Investigator must certify that the data entered into the Electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive a CD-ROM or paper copies of the patient data for archiving at the investigational site.

Data not requiring a separate written record will be defined in the Site Operations Manual and [Assessment schedule](#) and can be recorded directly on the CRFs. All other data captured for this study will have an external originating source (either written or electronic) with the CRF not being considered as source.

All data should be recorded, handled and stored in a way that allows its accurate reporting, interpretation and verification.

CRO working on behalf of Novartis will review the data entered into the eCRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to the CRO working on behalf of Novartis who will make the correction to the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent electronically to Novartis (or a designated CRO).

Randomization codes will be tracked using Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The database will be sent electronically to Novartis (or a designated CRO).

ABPM data will be collected by a designated CRO and the results will be sent electronically to Novartis and the data management CRO

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

The occurrence of any protocol deviations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and the treatment codes will be unblinded and made available for data analysis. Any changes to the database after that time can only be made by joint written agreement between the Global Head of Clinical Information Sciences and the Clinical Franchise Head.

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### **10.3 Data Monitoring Committee**

Not required.

### **10.4 Adjudication Committee**

Not required.

## **11 Data analysis**

All data analyses will be performed under the direction of Novartis personnel.

### **11.1 Analysis sets**

For all analysis sets, subjects will be analyzed according to the study treatment(s) received.

The full analysis set will include all subjects who received study treatment.

The safety analysis set will include all subjects that received any study drug.

The PK analysis set will include all subjects with available PK data and no protocol deviations with relevant impact on PK data.

The primary PD analysis set will include all subjects with available PD data. The secondary PD analysis set will include all subjects with available PD data and no protocol deviations with relevant impact on PD data.

### **11.2 Subject demographics and other baseline characteristics**

All data for background and demographic variables will be listed by treatment group and subject. Summary statistics (mean [or geometric mean for log transformed data]), standard deviation, minimum, median and maximum) will be provided by treatment group.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment group and subject.

All data for background and demographic variables will be listed by treatment sequence and subject. Summary statistics will be provided for all subjects, as well as for each treatment sequence.

Relevant medical history, current medical conditions, results of laboratory screens, drug tests and any other relevant information will be listed by treatment sequence and subject.

### **11.3 Treatments (study drug, rescue medication, other concomitant therapies, compliance)**

Data for study drug administration (rescue medication) and concomitant therapies will be listed by treatment group and subject.

## 11.4 Analysis of the primary variable(s)

The primary efficacy variable will be the change in the 12 hour average of systolic blood pressure measured by ambulatory blood pressure monitoring (ABPM) 28 days following the start of treatment.

### 11.4.1 Variable(s)

The primary efficacy variable will be the change in the 12 hour average of systolic blood pressure measured by ambulatory blood pressure monitoring (ABPM) 28 days following the start of treatment. This is defined as the 12 hour daytime average systolic blood pressure on day 28 minus the 12 hour daytime average systolic blood pressure on day -1.

### 11.4.2 Statistical model, hypothesis, and method of analysis

The primary efficacy variable will be the change in the 12 hour average of systolic blood pressure measured by ambulatory blood pressure monitoring (ABPM) 28 days following the start of treatment. Out-of-office ABPM is a more reliable measure of a patient's blood pressure than office-based BP readings which may be falsely elevated because of "white-coat" phenomena (Bakris et al 2010). The change from baseline in the placebo group will be compared to the change from baseline in the **pooled** LHW090 doses. The criteria to demonstrate efficacy (success) will be based on statistically significant (1-sided  $p<0.1$ ) greater reduction from baseline in mean daytime SBP with active treatment (pooled doses) than with placebo, as well as an estimated median reduction on active treatment (pooled active doses) of at least 7 mmHg higher than on placebo. The threshold of a 7 mmHg reduction in placebo-adjusted systolic BP by ABPM is considered clinically significant since similar magnitude changes were observed in a phase 3 trial of an endothelin-receptor antagonist, darusentan, for the same indication (Weber et al 2009).

Study patients will be randomized into one of 3 groups, placebo, 100 mg LHW090 and 200 mg LHW090, as an add-on therapy to conventional background anti-hypertensive therapy. 40 patients will be randomized to placebo, and 20 to each dose of active treatment. This will give around 32 completers in the placebo group and 16 on each active dose group. The primary analysis of change in mean daytime systolic blood pressure will be performed using the data collected during the period 0900 to 2100 consistent with recommendations from the European Society for Hypertension (O'Brien et al 2013). The average of these 12 hours of data will be produced using data from the baseline ambulatory blood pressure monitoring on Day -2 and Day 27. The change from baseline in mean daytime SBP will be estimated from a longitudinal model using all data collected for every patient until Day 27. The model will include fixed effects for baseline, treatment (including dose), and visit, and a random effect for each patient. This analysis is unbiased under the assumption that the data are missing at random (MAR).

### 11.4.3 Handling of missing values/censoring/discontinuations

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#### **11.4.4 Supportive analyses**

As a supportive analysis, the difference in efficacy between the two active doses will be examined by computing the t-statistic associated with the difference in means.

### **11.5 Analysis of secondary and exploratory variables**

The secondary objective variables are obtained from pharmacokinetic analyses, as described in [Section 11.5.3](#). These analyses of these data are described in this section.

#### **11.5.1 Efficacy / Pharmacodynamics**

There are no efficacy secondary variables.

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#### **11.5.2 Safety**

##### **Vital signs**

All vital signs data will be listed by treatment, subject, and visit/time and if ranges are available abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

##### **ECG evaluations**

All ECG data will be listed by treatment, subject and visit/time, abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

##### **Clinical laboratory evaluations**

All laboratory data will be listed by treatment, subject, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

##### **Adverse events**

All information obtained on adverse events will be displayed by treatment and subject.

The number and percentage of subjects with adverse events will be tabulated by body system and preferred term with a breakdown by treatment. A subject with multiple adverse events within a body system is only counted once towards the total of this body system.

### 11.5.3 Pharmacokinetics

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Descriptive summary statistics will be provided by treatment and visit/sampling time point, including the frequency (n, %) of concentrations below the LLOQ and reported as zero.

Summary statistics will include mean (arithmetic and geometric), SD, CV (arithmetic and geometric), median, minimum and maximum. An exception to this is Tmax where median, minimum and maximum will be presented. Concentrations below LLOQ will be treated as zero in summary statistics and for PK parameter calculations. A geometric mean will not be reported if the dataset includes zero values. Pharmacokinetic parameters will be calculated as described in [Section 8.5](#) and will be listed by treatment and subject. PK-PD relationships will be explored as relevant.

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### 11.5.4 Pharmacokinetic / pharmacodynamics interactions

The relationship between PK and key PD parameters may be explored using a graphical approach. Descriptive statistics may be provided. Corporate Confidential Information

### 11.5.5 Other assessments

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### **11.7 Power for analysis of key secondary variables**

There are no power analyses for the secondary safety variables.

### **11.8 Interim analyses**

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## **12 Ethical considerations**

### **12.1 Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

### **12.2 Responsibilities of the investigator and IRB/IEC**

Before initiating a trial, the investigator/institution should obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g. advertisements) and any other written information to be provided to subjects. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

For multi-center trials, a Coordinating Investigator will be selected by Novartis around the time of Last Patient Last Visit to be a reviewer and signatory for the clinical study report.

## **12.3 Publication of study protocol and results**

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

## **13 Protocol adherence**

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of subjects should be administered as deemed necessary on a case by case basis. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.

Investigators must apply due diligence to avoid protocol deviations. If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC/REB it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

### **13.1 Protocol Amendments**

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented, provided the Health Authorities and the reviewing IRB/IEC are subsequently notified by protocol amendment.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any subject included in this study, even if this action represents a deviation from the protocol. In such cases, the CTL should be informed and (serious) adverse event reporting requirements ([Section 9](#)) followed as appropriate.

## 14 References

Available upon request

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